I. STATUS OF THE APPLICATION

Claims 1-23 were filed in the original application. During prosecution of the application, claims 1-23 were cancelled and claims 24-44 were added in the Amendment and Response to Office Action filed January 8, 2003. Claims 24-44 were cancelled and claims 45-71 were added in the Amendment and Response to Office Action filed May 1, 2003. Claims 69 and 70 were cancelled in the Amendment and Response to Final Office Action filed July 7, 2004. Claims 45-68, and 71 were cancelled, and claims 72-107 were added in the Amendment and Response to Office Action filed February 17, 2005. Claims 72-107 were rejected in the Final Office Action dated May 10, 2005.

In an Appeal Brief filed November 9, 2005 the Applicant appealed the Final Office Action of May 10, 2005. In the Decision on Appeal mailed July 31, 2006 the Board of Patent Appeals and Interferences reversed all of the Examiner's rejections. The Office Action mailed September 12, 2006 was made in Response to the Board's rejections. Claims 108-112 were added in the Amendment and Response to Office Action of September 12, 2006. No claims were amended, cancelled or newly added in the Response to Office Action of June 18, 2007. In response to Applicant's Appellant's Brief filed in response to the Final Office Action of March 24, 2008, the Office has issued the Office Action of January 13, 2010. Therefore, Claims 72-112 are currently pending.

In the Office Action dated January 13, 2010, the Office has made three rejections. The currently pending rejections are:

1. Claims 72-105 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "LaDu, 1995") and LaDu (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991 (hereinafter "LaDu, 1991") and Pharmacogenetics (Chapter 4, pages 309-326) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol. 286, pages 487-491, October 1999) (hereinafter "Evans") in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42047, January,

1999) (hereinafter "Hacia") and further in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) (hereinafter, "Ahern") and Anderson *et al.* (US Pat 6,267,722, July 31, 2001) (hereinafter "Anderson") and further in view of Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller"), in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, pages 471-476, 1994) (hereinafter "Quane").

2. Claims 108-112 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "LaDu, 1995") and LaDu (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991 (hereinafter "LaDu, 1991") and Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol. 286, pages 487-491, October 1999) (hereinafter "Evans") in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42047, January, 1999) (hereinafter "Hacia") further in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) (hereinafter, "Ahern") and Anderson *et al.* (US Pat 6,267,722, July 31, 2001) (hereinafter "Anderson") and further in view of Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, pages 471-476, 1994) (hereinafter "Quane") or as applied to claims 72-107 and further in view of the specification (hereinafter "Specification") (Tables 1-4).

3. Claims 106-107 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "LaDu, 1995") and LaDu (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991 (hereinafter "LaDu, 1991") and Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol. 286, pages 487-491, October 1999) (hereinafter "Evans") in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21,

pages 42047, January, 1999) (hereinafter "Hacia") further in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) (hereinafter, "Ahern") further in view of Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, pages 471-476, 1994) (hereinafter "Quane").

II. STATUS OF THE REJECTIONS

A. Claims 72-105 are not obvious

1. The cited references do not teach all elements of the presently claimed invention

Applicant submits that the Office's combination of references fails to teach all elements of the claims. For example, none of the Examiner's references, alone or in combination, teach or suggest a computer program comprising instructions which direct a processor to analyze data derived **from use of said reagents**. In addition, various dependent claims further specify more specific details for how the computer program is configured, for example, claims 73-83, 85-100 and 102-105.

In the Office Action of January 13, 2010 the Office notes:

> "The response further asserts that the rejection fails to address the content of the kits instructions as provided in Claims 81-84, 101, 106, 107, for example. As noted above, the information provided in the form of instructions in a kit does not carry patentable weight, as held in Ngai." (Office Action of January 13, 2010, page 14.)

And:

> "While the response asserts that the Board's silence in the decision is acquiescing to applicant's position, this argument has been reviewed but is not persuasive, as

there is no indication of the Board's position on this matter or record." (Office Action of January 13, 2010, page 12.)

Applicant respectfully disagrees with the Office's rejection. First, claims 106 and 107 do not recite a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents. Second, and contrary to the Office's opinion, in its Decision the Board **clearly and expressly** recognizes a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents as a claim element. For example, in its Decision on Appeal mailed July 31, 2006, the Board of Patent Appeals and Interferences explicitly considered this element of claim 72:

> "Finally, the kit defined by claim 72 comprises "a computer program comprising instructions which direct a processor to analyze data derived from **use of said reagents**." (Decision on Appeal mailed July 31, 2006, page 5). (Emphasis added.)

Accordingly, the Board of Patent Appeals and Interferences concluded:

> "In our view, these disclosures (*i.e.*, of the Specification) reasonably support the concept of combining reagents for detecting variant alleles with **a computer program to analyze data indicating the presence or absence of such variant alleles**." (Decision on Appeal mailed July 31, 2006, page 8). (Emphasis added.)

And:

> "However, on page 4 of the Examiner's Answer, the examiner quotes the following passage from the specification: "In some embodiments, a computer based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician) e.g., probability of abnormal pharmacological

> response, presence of underlying disease, or differential diagnosis of disease) (emphasis added). While this passage does not use precisely the same words as claim 72, we agree with Appellant that it reasonably describes **the limitation recited in the claim**. (Decision on Appeal mailed July 31, 2006, page 6). (Underlining in original, bold emphasis added.)

In the Office Action of January 13, 2010 the Office improperly dismisses this limitation of the claims that has previously been expressly recognized and accepted by the Board of Appeals and Interferences. In this assertion the Office has made a number of errors.

First, the Board of Appeals and Interferences has already considered the Office's arguments with regard to *In re Ngai* (See, for example, Examiner's Answer mailed December 30, 2005, pages 18-22), and has found the Office's assertions non-persuasive. **The Office is bound by the Board's decision**. Surprisingly, in the Office Action of January 13, 2010 the Office notes "The Board does not provide any statements on In re Ngai that would be appropriate in considering the newly presented rejection, as above." (Office Action of March 24, 2008, page 10), despite the Board's consideration of In re Ngai as a matter of record, the Board's clear cut recognition of the limitation (see above), and there being no question that the limitation is missing from the Office's combination of references.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

Second, at the time of its Decision the Board of Patent Appeals and Interferences was in possession of a detailed consideration of *In re Ngai* in the Appellant's Reply Brief filed by the Appellant on March 3, 2006. In its Decision on Appeal of mailed July 31, 2006, the Board of Patent Appeals and Interferences does not rebut a single point or issue raised by the Appellant with regard to the inapplicability of *In re Ngai* to the prosecution of the present application. This fact was pointed out to the Office in the Appellant's Brief filed September 24, 2009, but in the Office Action of January 13, 2010 the Office fails to respond.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

Third, **the kits of the claimed invention are not "known kits**". This point was brought to the Office's attention in the Amendment and Response to Office Action Dated September 12, 2006, page 12, in the Response to Office Action Dated June 18, 2007, page 12, and in the Appellant's Brief filed September 24, 2009. In Office Action of January 13, 2010 the Office notes:

> "This argument has been reviewed but not convincing, because in light of the teachings in the art, the kits would have been obvious." (Office Action of January 13,2010, page 12.)

Applicant submits that the Office has never indicated where such "known kits" (*i.e.*, kits with the missing limitation) are to be found, other than in the present application. Accordingly, *In re Ngai*, wherein an applicant is precluded from substituting one set of instructions for another with the same previously disclosed product, **is irrelevant** to the presently claimed invention wherein such kits were clearly unknown at the time the invention was made.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

Fourth, the Office has never indicated where in the Office's references, either alone or in combination, such kits (*e.g.*, kits with "reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject") are to be found. In the Office Action of January 13, 2010 the Office notes:

> "Fourth, the response asserts the Examiner has not indicated where kits are to be found. This argument has been reviewed but is not convincing. Kits are routine in the art for simplicity. The examiner specifically included the Ahern reference to address applicants concerns that kits were not known at the time the invention was made." (Office Action of January 13, 2010, page 12.)

Applicant notes that whether or not the **kits of the presently claimed invention** are to be found in the Office's combination of references is at issue, not the presence or absence of **kits as a generic concept** in the art. Applicant submits that kits of the presently claimed invention are clearly not to be found in the Office's combination of references. Ahern teaches kits for, for example: expression of proteins from cloned genes; for labeling DNA or RNA probes with radioisotopes or fluorescent tags; for labeling oligonucleotides by conjugation with alkaline phosphatase; for small-scale purifications; for isolating cells from whole blood for cytotoxicity assays; for painting chromosomes with fluorescent dyes; for cryopreserving mouse embryos; and for signal transduction research.

Ahern does **not** teach or suggest kits sufficient to detect variation in one gene. Ahern does **not** teach or suggest kits sufficient to detect variation in two genes. Ahern does **not** teach or suggest kits sufficient to detect variation in two or more genes selected from a group of genes, or in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNA1S, MTHFR, MTR, MTRR, CB, TNFα and TNFβ.* These missing elements were pointed out to the Office in the Appellant's Brief filed September 24, 2009, page 22. In the Office Action of January 13, 2010 the Office is unresponsive to these facts. Indeed, to the extent that Ahern contemplates characterization of DNA, **Ahern discourages use of such kits:**

> "Some tasks … such as constructing genomic libraries, designing primer sets for sequencing, or synthesizing nucleic acids or peptides … are so daunting that for many scientists it makes more sense to hire out." (Ahern, page 5).

In the Office Action of January 13, 2010 the Office misconstrues Ahern's simple and unambiguous statement:

> "The response argues that Ahern discourages use of kits (see page 23 of response filed September 24, 2009. This argument has been reviewed but is not persuasive. Reviewing the complete disclosure of Ahern specifically encourages commercialization of kits so scientists can quickly, cheaply order the necessary reagents for a particular method." (Office Action of January 13, 2010, page 13.)

Applicant notes that the Office's arguments and speculations regarding "commercialization", quickness or cheapness fail to address the simple fact that Ahern clearly directs scientists away from kits for the specific purpose of the claims *i.e.,* Ahern directs scientists to hire others for DNA characterization rather than to use kits. Accordingly, the Office's reference teaches directly away from both the Office's combination of references, and from the presently claimed invention.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

Fifth, the Office confuses the printed matter instructions of *In re Ngai* with a computer program comprising instructions which direct a processor to analyze data derived from **use of said reagents** of the claims. As pointed out to the Office (Appellant's Brief of September 24, 2010, page 23), computer instructions which direct a processor to analyze data for generating a perioperative genomic profile for a subject as claimed, qualify as statutory subject matter because storage of the computer instructions turns a computer readable medium into a functional component which directly cooperates with the processor. Computer instructions cause computer functions to occur, and are therefore inarguably functional components of the computer system. These **facts** have been acknowledged by the Board of Appeals and Interferences, and are uncontested in the Office Action of January 13, 2010.

To the contrary, in the Office Action of January 13, 2010 the Office notes:

> "Applicant's fifth argument is directed to the printed matter of In re Ngai vs. the computer program comprising instructions directing a processor to analyze data derived from such reagents. This argument has been reviewed but is not persuasive. The instructions as intended use in the kit of Ngai and the instructions on a computer program as intended use in the instant applications are analogous. Applicant appears to be attempting to place instructions in a different format, i.e. a computer to frustrate the intent of Ngai." (Office Action of January 13, 2010, page 13.)
>
> And:
>
> "As noted above, the information provided in the form of instructions in a kit does not carry patentable weight, as held in Ngai." (Office Action of January 13, 2010, page 14.

Applicant submits that the Board has previously recognized that the computer programs of the presently claimed invention are patentable subject matter. Accordingly, the computer programs of the presently claimed invention are clearly not analogous to Ngai's "instructions of intended use", or the Office's "instructions on a computer program as intended use". Nor do the computer programs of the presently claimed invention "frustrate the intent of Ngai". As pointed out to the Office:

> "Contrary to the Examiner's misinterpretation, *In re Ngai* does <u>not</u> address, consider or even mention computers, computer programs, computer programs comprising instructions, or computer analysis of data." (Appellant's Brief of September 24, 2009, page 25.) (Emphasis in original).

In turn, Applicant submits that the Office's addition of Anderson does not remedy the multiple defects of the Office's combination of 7 other references. For example, Anderson does not teach or suggest a computer program comprising instructions which direct a processor to analyze data derived from **use of said reagents** configured such that

when exposed to a sample containing target nucleic acid from a perioperative subject, the subject being a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject. These facts were brought to the Office's attention in the Appellant's Brief filed September 24, 2009, page 25. In the Office Action of January 13, 2010 the Office fails to respond to these facts.

For at least these reasons, and as accepted by the Board of Appeals and Interferences, "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents" (*i.e.*, not merely any computer program that the Office is able to locate in the alleged prior art) is **a proper and statutory element of claims 72-105**. None of the Office's references, alone or in combination, teach or suggest this element. In turn, none of the Office's references, alone or in combination, teach or suggest the limitation "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents to indicate an anesthesia treatment course of action." (Independent claim 84.) As well, none of the Office's references, alone or in combination, teach or suggest the limitation "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents to indicate a surgical treatment course of action." (Independent claim 101.) These missing elements were pointed out to the Office in the Appellant's Brief of September 24, 2009, pages 25-26. The Office Action of January 13, 2010 is unresponsive to these facts.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

As well, in the Office Action of January 13, 2010 the Office fails to address elements of dependent claims that are missing from the Office's combination of references. For example, in order to establish prima facie obviousness, the Office must point to a reference, or combination of references, that teaches or suggests a computer program with software that analyzes **data from the kit of the claimed invention**, and

generates, for example, recommendations for treatment options based on the presence or absence of variant alleles in *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ*. The Office has **never** identified such a computer program in the cited references taken alone, or in combination. Nowhere in the Office's cited references is knowledge of variant alleles in two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ* combined to indicate an anesthesia treatment course of action (claim 84), a surgical treatment course of action (claim 101), a specific clinical pathway of medical intervention (claim 106), or a specific clinical pathway or anesthesia intervention (claim 107). None of the Office's references teach or suggest how to perform, or even whether to perform, the combination of data from the claimed variant alleles, and translation of this data into a subject-specific treatment course of action. These missing elements were pointed out to the Office in the Appellant's Brief of September 24, 2009 pages 26-27. The Office Action of January 13, 2010 is unresponsive to these facts.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

Nor do the Office's cited references teach or suggest a computer program that directs the fate of the genetic data according to the subject's preference (claim 82), or that directs a user to a specific perioperative clinical pathway for a subject (claim 83). None of the rejection's references teach or suggest kits with reagents sufficient to detect variant alleles in *F5, F2, CACNA1S, MTR, MTRR,* and *CBS*. What is missing from the Office's references is a disclosure of, for example, primers and probes specific to these genes and these alleles. None of the Office's references, alone or in combination, teach or suggest **kits sufficient to detect the presence or absence of variant alleles in two or more genes**, or even kits sufficient to detect of the presence or absence of variant alleles in a single gene. These missing elements were pointed out to the Office in the Appellant's Brief of September 24, 2009, page 27. The Office Action of January 13, 2010 is unresponsive to these facts.

Because the Office's references individually, and in combination, fail to teach all elements of claims 72-105, and indeed teach away from one another, Applicant submits that the Office has failed to establish the *prima facie* obviousness of the claims.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

2. There is no motivation to combine the references in the manner indicated by the Office

The Supreme Court in *Graham* established specific steps for a non-obvious analysis: (1) determine the scope and content of the prior art; (2) evaluate the differences between the prior art and the claims at issue; and (3) determine the level of ordinary skill in the art.[1] "Against this background, the obviousness or non-obviousness of the subject matter is determined."[2] These *Graham* steps provide a subjective analysis of whether an invention was obvious at the time it was made. Objective evidence, termed "secondary consideration" evidence, that an invention was not obvious at the time it was made also may be introduced.[3] Such secondary consideration evidence could include, for instance, the commercial success of an invention or that the invention filled a long-felt need. The Supreme Court recognized the use of secondary consideration evidence in *Graham* in an effort to "guard against slipping into use of hindsight."[4] The Federal Circuit has followed this holding and ruled that it is "error to exclude [secondary consideration] evidence from consideration."[5] In an effort to achieve this goal, courts have recognized a variety of types of secondary consideration evidence, including: long-felt need,[6] commercial success,[7] the failure of others to achieve the invention,[8] licensing by others,[9] and unexpected results or advantages.[10]

Thus, the non-obvious standard of §103(a) requires the Examiner to make a historical judgment: whether the invention would have been obvious at the time the invention was made in the past. To reach a proper non-obvious conclusion, the Office

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[1] See *Graham*, 383 U.S. at 17.
[2] Id.
[3] *Id.* at 17-18.
[4] *Id.* at 36 (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.*,332 F.2d 406, 412 (1964)).
[5] *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983).
[6] *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000)
[7] *Id.* at 1377-1378.
[8] *Id.* at 1378-1379.
[9] *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed.Cir. 2000).
[10] *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1382–83 (Fed.Cir. 1986).

must not only step backward in time to a moment when the invention was unknown, but also avoid letting knowledge that the invention was achieved affect the Office's decision about whether it was obvious at the time it was achieved.[11] The courts have recognized that meeting this standard "requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."[12]

In an effort to preclude such an improper result, the Federal Circuit requires that the non-obvious analysis be conducted viewing the invention as a whole.[13] Using "'hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention'"[14] or conducting a "reference-by-reference, limitation-by-limitation analysis" fails to demonstrate how the invention is obvious in light of prior art.[15] Similarly, the Examiner may not use the invention as a blueprint for linking together pieces of prior art in order to find the invention obvious.[16] The Federal Circuit has referred to using the invention as a "blueprint for piecing together the prior art . . . [as] the essence of hindsight."[17]

Applicant submits that the Office has clearly and improperly utilized hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is prima facie obvious. Applicant contends that, at the time the invention was made, there existed no explicit or implicit teaching or suggestion or motivation to combine elements present in the art to generate the presently claimed invention. Prior to the disclosure of the present invention, there existed no teaching, from anywhere, regarding the kits and computer programs of the presently claimed invention.

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[11] *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)

[12] *In re Dembiczak*, 175 F.3d at 999 (emphasis added); see also *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("It is difficult but necessary that the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.").

[13] See *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004).

[14] *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (quoting *In re Fine*, 837 F.2d 1071, 1075 (1988)).

[15] *Id.*, at 1374

[16] *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

[17] *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)

Applicant submits that the Office has inappropriately utilized the disclosure of the invention in an attempt to recreate the invention. In the Office Action of January 13, 2010 the Office argues:

> "Quane et al (herein referred to as Quane) teaches the detection of novel mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalational anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases. . . . Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of mutations (page 474, col.2).
>
> Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the necessary reagents for sampling patients prior to subjecting the patient to anesthetics for the presence of alleles within CYP2D6, or BCHE genes which cause resistance to the drug succinylcholine, resistant to succinycholine, debrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics of Evans, and thus avoiding any fatal reaction to anesthesia for example." (Office Action of January 13, 2010, pages 7-8.)

Applicant respectfully disagrees with the Office's rejection. Applicant notes that in the Office Action of January 13, 2010 the Office fails to explain the relevance of the Quane reference. For example, none of the claims of the presently claimed invention recite the ryanodine receptor gene (RYR1). As well, none of the claims of the presently claimed invention recite the RYR1 Gly341Arg mutation. Accordingly, in the Office Action of January 13, 2010 the Office fails to indicate why an artisan of ordinary skill seeking to test for mutations in genes encoding BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ would turn to Quane for guidance.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

Moreover, the Quane reference merely suggests testing for a **single** disorder (*i.e.*, malignant hyperthermia) in a **single** gene (*i.e.,* they ryanodine receptor gene RYR1) **after** a patient has had a prior complication during a surgical procedure. In the Office Action of January 13, 2010 the Office notes:

> "In summary, the prior art teaches: . . .
> Once a mutation is known to be associated with negative response to anesthesia or drugs, patients with the mutation can avoid the negative response (Quane.)" (Office Action of January 13, 2010, page 10.)

In the Office Action of January 13, 2010 the Office **fails to cite or indicate in anyway where this teaching is to be found in Quane**. The Office Action of January 13, 2010 notes:

> "Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2)." (Office Action of January 13, 2010, page 7.)

However, Quane at page 471, col. 2 refers to the magnitude of contractions induced in strips if muscle tissue in vitro by caffeine and halothane i.e., the in vitro contracture test (IVCT), **not** DNA testing:

> "Over 40 individuals who have survived a clinical episode of MH have been diagnosed by the European IVCT and have been diagnosed as MHS (88% of probands) or MHE (12% of probands) (6). Once an individual is diagnosed as being susceptible to MH the anaesthetics which trigger this syndrome can be avoided." (Quane, page 471, col. 2.)

Thus, Quane describes clinical testing for MH susceptibility by the in vitro contracture test (IVCT), *i.e.,* **not** DNA-based testing, **after** surviving a clinical episode of MH, *i.e.,* **not** before exposure.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Office Action of January 13, 2010 the Office notes:

> "Thus, the ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Acta Anaesthesiologica Scandinavica, LaDu, Pharmacogenetics, or Evans and Hacia and Hoon which are necessary for determining the genotypes of BchE and CYP2D6 which are associated poor reactions to anesthesia into a kit, as taught by Ahern for the express purpose of saving time and money and included a computer program taught by Anderson for the digitization, integration and convenience of patient information, and risk index." (Office Action of January 13, 2010, page 10).

At multiple points in the Office Action of January 13, 2010 the Office acknowledges the advantages of the presently claimed invention, and identifies one of ordinary skill in the art as a clinician. Moreover, the Office expressly recognizes an anesthesiologist as one of ordinary skill in the art:

> "The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed **the anesthesiologist** to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise." (Office Action of January 13, 2010, page 9.) (Emphasis added.)

> And:

> "Combining more than one screening method to determine the genomic profile of a patient would have provided **the anesthesiologist** with a more complete picture of the patient's genetic make-up." (Office Action of January 13, 2010, pages 9-10.) (Emphasis added.)

Accordingly, the Applicant submits that the Examiner's speculations and conclusory statements regarding the motivation and common sense of the ordinary artisan anesthesiologist to combine the claim elements to yield the claimed invention are unsupported by proper evidence, and are in error.

In the Office Action of January 13, 2010 the Office notes:

> "While the Examiner agrees that an anesthesiologist may be one of ordinary skill in the art, the Examiner also recognizes Quane, AAS, LaDu, Evans and Port [sic] as one of skill in the art. Quane clearly recognized the benefit of testing an individual prior to surgery to avoid triggering MH. However, the skilled artisan would encompass molecular biologists studying the relevant relationships. Thus, the skilled artisan would have been aware of the solution, as evidenced by the articles by molecular biologists." (Office Action of January 13, 2010, page 17.)

Applicant submits that the Office's rejection contains multiple errors. First, Poort is not cited as a reference in the rejection. Second, as noted above, the Office fails to provide the relevance of Quane to the claims of the presently claimed invention. Third, as noted above, Quane refers to in vitro **contracture testing** of biopsied skeletal muscle **after** a deleterious clinical event, not genetic testing before exposure to anesthetic drugs. In the Office Action of January 13, 2010 the Office fails to indicate where this teaching is to be found in Quane.

As well, in constructing its hybrid or alternative artisan of ordinary skill *i.e.* an anesthesiologist combined with or in place of a molecular biologist, the Office makes multiple errors. First, in the Office Action of January 13, 2010 the Office fails to cite statute or case law supporting the Office's speculative creation of an anesthesiologist/molecular biologist artisan of ordinary skill. Nor has the Office

indicated where such artisans of ordinary skill, let alone of extraordinary skill, are to be found in the Office's combination of references. Second, the Office fails to consider the claims of the present invention from the perspective of either an anesthesiologist, or a molecular biologist, or the Office's imagined anesthesiologist/molecular biologist at the time the invention was made. Different aspects of the rejection float from one artisan to another. This is improper. The rejection must identify who the artisan is and their requisite skill level. The necessity for this is demonstrated by the fact that the rejection uses inconsistent perspectives at each different turn.

Applicant asserts that the Office's failure to identify an artisan of ordinary skill of relevance to the claims of the presently claimed invention is explained by the wide separation between anesthesiology and genome based medicine. Applicant submits herewith Appendix A "Perioperative Genomics: Anesthesiology Goes Molecular", GenomeLife Magazine, issue 3, November, 2003, page 7. (available at www.genome.duke.edu) (hereinafter "GenomeLife"). GenomeLife notes:

> "According to Schwinn and a growing contingent of forward-thinking anesthesiologists, the tools of "perioperative genomics" may soon be a standard part of the operating-room arsenal used to ensure patient safety. The idea is simple: since millions of common variants (polymorphisms) in our DNA have been catalogued, it should now be possible to examine specific DNA changes in order to predict negative surgical outcomes such as intraoperative bleeding. While the concept may be intriguing, **it is still in its infancy**. A Google search of "perioperative genomics" yields less than two dozen hits (most of those are links to Schwinn and Duke); even a query of the PubMed database generates a mere smattering of scientific references. In part, this is due to the novelty of this approach, but its failure to make much of a splash thus far also reflects **a long-standing separation of the practice of anesthesiology from clinical genetics and genome-based medicine.** Schwinn believes that this divide arose from how traditional anesthesiology is done "in the trenches" as compared to genetics." (GenomeLife, page 7, col. 1.) (Emphasis added.)

And:

> Looking ahead, Schwinn marvels at the untapped potential of perioperative genomics if it is done right. "If we are both careful and visionary, these types of studies can help us predict perioperative outcomes based on preoperative genomic information. **They could truly revolutionize clinical research**." (GenomeLife, page 7, col. 2.) (Emphasis added.)

Thus, even well after the filing date of the presently claimed invention, the field was "still in its infancy", and not, as the Office argues, in the possession of the Office's artisan of ordinary skill. Similar to Office's impermissible combination of references made in hindsight, Applicant submits that the Office has engaged in assembling an impermissible combination of ordinary artisans in hindsight.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Response to Office Action Dated June 18, 2007 Applicant submitted the Declaration of Dr. Kirk Hogan. In his Declaration, Dr. Hogan (Declaration of Kirk Hogan M.D. Under 37 C.F.R. 1.132, pages 2-3.) explains that prior to the perioperative genomic profile kits of the presently claimed invention, **anesthesiologists of ordinary skill** were **not** aware of, and did **not** use, **kits for genomic analysis** of single or multiple polymorphisms, genes or diseases. Dr. Hogan explains that:

> "5. For many decades before the perioperative genomic profile kits of the present patent application, anesthesiologists were highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations. Nevertheless, anesthesiologists did not arrive at the kits of the presently claimed invention."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "6. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of single polymorphisms, single genes or single diseases."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "7. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of single polymorphisms, single genes or single diseases.

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "8. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "9. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "11. While the anesthesiologist of ordinary skill has for many decades recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery, anesthesiologists of ordinary skill could not have combined the claimed elements because they lacked the

> requisite appreciation of the technical knowledge to arrive at the perioperative genomic profile kits of the presently claimed invention as a solution to the problems addressed by the presently claimed invention."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Nevertheless, in the Office Action of January 13, 2010 the Office responds:

> "Here the declaration **does not appear to provide any evidence**." (Office Action of January 13, 2010, page 15.) (Emphasis added.)

> And:

> "The declaration appears to be focusing on the fact that anesthesiologists did not arrive at the kits. However, the standard required is that one of skill in the art. One skilled in the art would encompass molecular biologists who were performing association studies between polymorphisms and poor reactions to anesthesiology." (Office Action of January 13, 2010, page 16.)

Applicant notes that expert testimony must be considered, and the testimony that is not simply an expression of an ultimate legal conclusion **is** evidence that cannot be summarily dismissed. Applicant submits that in its conclusions the Office has made a number of errors. First, the proper standard is one of ordinary skill in the art, not one of exceptional skill *i.e.*, a researcher or an author of an academic manuscript. Second, elsewhere in the Office Action of January 13, 2010 the Office clearly establishes an anesthesiologist as an artisan of ordinary skill for the purposes of performing an obviousness analysis. (See Office Action of January 13, 2010, pages 9-10.) It is improper for the Office to switch the identity of the skilled artisan to support an argument when convenient (*i.e.*, when but for the switch, the argument would fail). **This is a fundamental error in the rejection.**

Third, even if a molecular biologist could be considered an artisan of ordinary skill, and Applicant submits that one could not, the Office provides no evidence that such

a molecular biologist would have been motivated to make the Office's combination and thereby arrive at the claims of the present invention. For example, the Office has made no showing that a molecular biologist of ordinary skill would have been motivated to combine reagents configured to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β with a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents. Indeed, this is contrary to the art and the evidence in the record. Molecular biologists of ordinary skill did not and would not assemble the clinically relevant claimed markers or provide software to analyze them.

Applicant submits that Dr. Hogan's Declaration provides **clear-cut, expert, and uncontested evidence** that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations "**for many decades**", and that despite this motivation artisans of ordinary skill of any background failed to achieve the presently claimed invention at the time the invention was made. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Response to Office Action of June 18, 2007 Applicant submitted the Declaration of Dr. Douglas Baird Coursin. In his Declaration, Dr. Coursin explains that there was no suggestion or teaching in the prior art for periperative genomic profiles. Dr. Coursin further explains the **long felt and unmet need** for this solution to the problem of inborn predispositions to complications during anesthesia and surgery, and the unexpected success of the technology. Dr. Coursin is one of the leading anesthesiologists in the country, and has been for many years. Dr. Coursin explains that skilled artisans, such as anesthesiologists, have as a primary mission to solve the problem solved by the present invention. Yet even with this long-felt need and years of searching by innumerable practitioners, no one solved this long-felt need using the approach of the

present invention. In the Office Action of January 13, 2010 the Office does not contest or even address these facts.

In a situation like the present one, there may be no better evidence of non-obviousness than the **failure of an entire field** to solve their primary problem, even with a wealth of information and technology known in the literature. As Dr. Coursin notes:

> "However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made." (Declaration of Douglas Baird Coursin, M.D. Under 37 C.F.R. 1.132, page 3.)

In the Office Action of January 13, 2010 the Office does not contest or even address these facts. The Office takes the position that, even in view of these facts of record, there was no long felt need. However, the Office provides no evidence, references, expert testimony or reasoning in support of its conclusory and inaccurate speculation. Applicant notes that the field failed to realize the solution because the solution was **not obvious** to skilled artisans. Skilled artisans would not, and did not, see the combination the Office proposes that they should have and would have seen.

In the Office Action of January 13, 2010 the Office responds:

> "Similar to the declaration provided by Dr. Hogan, the declaration under 37 C.F.R. 1.132 filed December 18, 2007 is insufficient to overcome the rejection of claims as set forth in the last office action because: It states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. (Office Action of January 13, 2010, page 18.)

To the contrary, the Applicant submits that Dr. Coursin's Declaration provides **clear-cut, expert, and uncontested evidence** that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations for 26 years "and well before". Dr. Coursin's Declaration provides evidence that the need was persistent and recognized by those of ordinary skill in the art.

Applicant submits that the Office's rejection is based on hindsight knowledge of the invention wherein the Office has assumed what skilled artisans ***should have*** thought of the invention in view of numerous disparate pieces of prior art. In making the rejection, the Office (*i.e.*, not one of skill in the art, and who is in possession of hindsight knowledge of the invention), has *seen* an invention that the entire world of skilled artisans, focused for many years on the exact problem solved by the invention, had failed to see. Artisans, of ordinary and extraordinary skill in the field, who have devoted their careers to solving this problem, failed to put together the Office's combination of references, and failed to solve the problem. **The only logical explanation is that the invention is non-obvious.** In the Office Action of January 13, 2010 the Office does not contest or even address these facts.

Notably missing from the Office's rejection is placement in the hands and minds of the appropriate skilled artisans of: 1) the prior art of record (is this the type of work one skilled in the art would have reviewed in assessing the problem?); and 2) the mental and experimental process for modifying the art to arrive at the invention (even if they would have reviewed the cited art, would they have put the pieces together and modified the pieces appropriately?). At no point in the Office Action of January 13, 2010 does the Office provide **evidence** of the handling of the references in the hands and minds of the **appropriate skilled artisan**. Regardless, even if the Office had done this, the evidence of long-felt but unresolved need demonstrates that skilled artisan did not, and would not, arrive at the invention. If it were obvious, they would have done it years before the filing of the present application. In the Office Action of January 13, 2010 the Office does not contest or even address these facts.

The Supreme Court specifically states:

> "Often it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; **and the background knowledge possessed by a person having ordinary skill in the art**, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." (*KSR Int'l Co. v. Teleflex, In.,* 550 U.S., 127 S. Ct. 1727 (2007).) (Emphasis added.)

Applicant asserts that in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of **10** prior art elements (*vs.* 2 prior art references in *KSR v. Teleflex*), the Office has clearly failed to identify the reason why a person of ordinary skill in the art would have made the combination in the manner claimed. In making such a reconstruction, the Office may only take into account the common knowledge which was within the level of ordinary skill at the time the claimed invention was made, and may not include, as here, knowledge gleaned only from the Applicant's disclosure or unsupported assumptions about the mindset of the skilled artisan. (See *In re McLaughlin*, 443 F/2d 1392, 170 USPQ 209 CCPA, 1971.) The determination of whether a combination is a predictable variation of the prior art must be evaluated from the perspective of the person of ordinary skill in the art at the time claimed invention was made. Dr. Hogan's and Dr. Coursin's Declarations provide material evidence that Office's speculations regarding the level of ordinary skill are in clear error. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Office Action of January 13, 2010 the Office notes:

> "With respect to kits, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come prepared." (Office Action of January 13, 2010, page 5.)

In relying upon these arguments to support a prima facie case of obviousness, the Office has made a number of errors. First, The Office's acknowledgment of the benefits of the claimed invention made after the Office was in possession of the specification and claims does not, and cannot, substitute for substantial **evidence** of what an artisan of ordinary skill would or would not have been motivated to do at the time the invention was made. To the contrary, in the Office Action of January 13, 2010 the Office improperly persists in asserting new standards of the ordinary artisan's motivation to combine references *i.e.*, to "save time and money", and "to avoid any fatal reaction." In *In re Sang Su Lee* the Court of Appeals for the Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Office.[18] On multiple occasions in the prosecution of the present application the Examiner has had the opportunity to address this holding, and has never done so. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts. Applicant submits that the Office's improper combination of references, and failure to respond to numerous facts in the Appellant's Brief filed in response to the Final Office Action of March 24, 2008 preclude a finding of prima facie obviousness of the claims.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

B. Claims 108-112 are not obvious

Applicant submits that the Office has failed to establish a prima facie case of obviousness because: 1) the Office has erred in determining the scope and contents of the prior art and in ascertaining differences between the prior art and the claims at issue; 2) the cited references do not teach or suggest all elements of the presently claimed invention; and 3) the Office has not provided a motivation to combine the references. Applicant notes that claims 108, 109 and 110 depend from independent claims 72, 84 and 101 respectively, and are not obvious for at least the same reasons that claims 72, 84 and

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[18] *In Re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002).

101 are not obvious (see above). As well, claims 111 and 112 depend from independent claims 106 and 107 and are not obvious for at least the same reasons that claims 106 and 107 are not obvious (see below).

1. The Office has erred in not properly determining the scope and contents of the prior art, and in ascertaining differences between the prior art and the presently claimed invention

In the Office Action of January 13, 2010 the Office concedes:

"AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia, Ahern, Anderson, Miller and Quane do not specifically teach profiling of each of BchE, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CTP2 (sic), TNFA and TNFB. However, the instant specification teaches markers in each of these genes which are associated with various operative related disorders (see pages 55-57 of the specification reproduced below, Tables 1-5). The specification clearly illustrates genes and mutations which are associated with particular mutations in the prior art. The specification thus provides references for BChe, CYP2D6, MTHFR, MTR, CBS, MTRR, F5, F2 (prothrombin), CACNA1S, TNFa and TNFb. . . . The response filed March 26, 2001 in the parent application specifically illustrates that the invention does not claim discovery of newly identified sequences (page 7). . . .

Therefore, it would have been obvious in view of the teachings of the references from the specification, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia to include the recited genes along with additional genes on the array of Hacia for the high throughput analysis of operatives (sic) complications. The ordinary artisan would have desired to compile all known genes that are associated with operative complications on a high throughput array to detect mutations known to affect decisions.

Response to Arguments

> The response traverses the rejection. The response asserts the rejection fails to teach all of the limitations for the reasons discussed above. This argument has been considered but is not convincing for the reasons provided above. Thus for the reasons above and those already of record, the rejection is maintained." (Office Action of January 13, 2010, pages 26-27.)

Applicant submits that the Office has failed to establish a prima facie case of obviousness because the Office has erred in determining the scope and contents of the prior art, and in ascertaining differences between the prior art and the claims at issue. For example, contrary to the Office's characterization, claims 108-112 do not recite component parts sufficient to detect the presence or absence of variant alleles in *RYR1*. Accordingly, in the Office Action of January 13, 2010 the Office does not express the relevance of the Quane reference to the kits of the presently claimed invention.

As well, the Office Action of January 13, 2010 the Office fails to express the relevance of the Miller reference to the kits of claims 108-112.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

2. The cited references do not teach all elements of the presently claimed invention

Applicant submits that the Office's combination of references fails to teach all elements of the claims. For example, none of the Office's references, alone or in combination, teach or suggest the element of reagents that are sufficient to detect the presence or absence of variant alleles **in each of** *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β (*i.e.*, none provide the claimed **combination**). Applicant submits that the Office Action of January 13, 2010 fails to examine, or even recognize, this element of claims 108-112, or to explain why the claimed combination itself is obvious compared, for example, to other combinations.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

Moreover, Applicant submits that the Office's combination of references fails to teach or suggest all elements of the independent claims upon which claims 108-112 depend. For example, in the Office Action of January 13, 2010 the Office is explicit in its reason for providing Anderson:

> "Moreover, including a computer program for the expected benefits of digitizing, processing and inputting the information into the medical diagnosis expert system where it may be integrated with other patient information." (Office Action of January 13, 2010, pages 11-12.)

Applicant submits that although the Office is explicit in its reason for providing Anderson, it fails to remedy the missing elements of the Office's combination of references. For example, a missing element in the Office's combination of references is **not** a generic computer for obtaining data, synthesizing the data and then outputting information. Rather, a missing element in the Office's combination of references is a computer program comprising instructions which direct a processor to analyze data derived from use of **said reagents** in the kits of the presently claimed invention *i.e.*, reagents that are sufficient to detect the presence or absence of variant alleles **in each of** *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β. Applicant submits that the Office Action of January 13, 2010 fails to indicate where in the Office's combination of references, these missing elements are to be found.

Furthermore, in the Office Action of January 13, 2010 the Office fails to explain the relevance of Anderson to claims 111 and 112 which depend from claims 106 and 107, respectively.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

3. There is no motivation to combine the references in the manner indicated by the Office

Applicant submits that in the Office Action of January 13, 2010 the Office has failed to provide a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements, *i.e.*, reagents that are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β, in the way the claimed new invention does *i.e.*, the kits of claims 108-112. For example, the Office fails to express why an artisan of ordinary skill would have been motivated to combine the teachings of AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia, Miller and Quane with Anderson to arrive at the kits of the presently claimed invention. Only through improper hindsight has the Office pieced together disparate references to compile the claimed **set** of markers. No proper motivation has been provided to explain why **the specific set of claimed markers** would be assembled for analysis as opposed to the innumerable number of other possible combinations of markers in the literature. Clearly, Anderson does not teach or suggest the kits of the presently claimed invention, or a kit of any kind. As well, Anderson does not teach or suggest instructions on a computer medium for use with a kit. Accordingly, in the Office Action of January 13, 2010 there is no explicit or implicit teaching or suggestion or motivation why an artisan of ordinary skill would turn to Anderson to generate the kits of claims 108-112. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts. Applicant submits that the Office's improper combination of references, and failure to respond to numerous facts in the Appellant's Brief filed in response to the Final Office Action of March 24, 2008 preclude a finding of prima facie obviousness of the claims.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

C. Claims 106 and 107 are not obvious

Applicant submits that the Office has failed to establish a prima facie case of obviousness because: 1) the Office has not provided a motivation to combine the

references; and 2) the cited references do not teach or suggest all elements of the presently claimed invention.

1. There is no motivation to combine the references in the manner indicated by the Office

Applicant submits that the Office has clearly and improperly utilized hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is prima facie obvious. Applicant contends that, at the time the invention was made, there existed no explicit or implicit teaching or suggestion or motivation to combine elements present in the art to generate the presently claimed invention. Prior to the disclosure of the present invention, there existed no teaching, from anywhere, regarding the kits and computer programs of the presently claimed invention.

Applicant submits that the Office has inappropriately utilized the disclosure of the invention in an attempt to recreate the invention. In the Office Action of January 13, 2010 the Office argues:

> "Quane et al (herein referred to as Quane) teaches the detection of novel mutations in ryanodine receptor gene (RR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalational anesthetics. Quane has identified Gly341Arg mutation which accounts for approximately 10% of Caucasian MHS cases. . . . Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of mutations (page 474, col.2).
>
> Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the necessary reagents for sampling patients prior to subjecting the patient to anesthetics for the presence of alleles within CYP2D6, or BCHE genes which cause resistance to the drug

> succinylcholine, resistant to succinycholine, debrisoquine hydroxylase, as taught by Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics of Evans, and thus avoiding any fatal reaction to anesthesia for example." (Office Action of January 13, 2010, pages 32-33.)

Applicant respectfully disagrees with the Office's rejection. Applicant notes that in the Office Action of January 13, 2010 the Office fails to explain the relevance of the Quane reference. For example, none of the claims of the presently claimed invention recite the ryanodine receptor gene (RYR1). As well, none of the claims of the presently claimed invention recite the RYR1 Gly341Arg mutation. Accordingly, in the Office Action of January 13, 2010 the Office fails to indicate why an artisan of ordinary skill seeking to test for mutations in genes encoding BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ would turn to Quane for guidance.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

Moreover, the Quane reference merely suggests testing for a single disorder (*i.e.*, malignant hyperthermia) in a single gene (*i.e.,* they ryanodine receptor gene RYR1) **after** a patient has had a prior complication during a surgical procedure. In the Office Action of January 13, 2010 the Office notes:

> "In summary, the prior art teaches: . . .
> Once a mutation is known to be associated with negative response to anesthesia or drugs, patients with the mutation can avoid the negative response (Quane.)" (Office Action of January 13, 2010, page 35.)

In the Office Action of January 13, 2010 the Office **fails to cite or indicate in anyway where this teaching is to be found in Quane**. The Office Action of January 13, 2010 notes:

> "Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2)." (Office Action of January 13, 2010, page 32.)

However, Quane at page 471, col. 2 refers to the magnitude of contractions induced in strips if muscle tissue in vitro by caffeine and halothane i.e., the in vitro contracture test (IVCT), **not** DNA testing:

> "Over 40 individuals who have survived a clinical episode of MH have been diagnosed by the European IVCT and have been diagnosed as MHS (88% of probands) or MHE (12% of probands) (6). Once an individual is diagnosed as being susceptible to MH the anaesthetics which trigger this syndrome can be avoided." (Quane, page 471, col. 2.)

Thus, Quane teaches clinical testing for MH susceptibility by the in vitro contracture test (IVCT), *i.e.,* **not** DNA-based testing, **after** surviving a clinical episode of MH, *i.e.,* **not** before exposure.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Office Action of January 13, 2010 the Office notes:

> "Thus, the ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Acta Anaesthesiologica Scandinavica, LaDu, Pharmacogenetics, or Evans and Hacia and Hoon which are necessary for determining the genotypes of BchE and CYP2D6 which are associated poor reactions to anesthesia into a kit, as taught by Ahern for the express purpose of saving time and money." (Office Action of January 13, 2010, page 35).

At multiple points in the Office Action of January 13, 2010 the Office acknowledges the advantages of the presently claimed invention, and identifies one of

ordinary skill in the art as a clinician. Moreover, the Office expressly recognizes an anesthesiologist as one of ordinary skill in the art:

> "The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed **the anesthesiologist** to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise." (Office Action of January 13, 2010, page 34.) (Emphasis added.)
>
> And:
>
> "Combining more than one screening method to determine the genomic profile of a patient would have provided **the anesthesiologist** with a more complete picture of the patient's genetic make-up." (Office Action of January 13, 2010, pages 34-35.) (Emphasis added.)

Accordingly, the Applicant submits that the Examiner's speculations and conclusory statements regarding the motivation and common sense of the ordinary artisan anesthesiologist to combine the claim elements to yield the claimed invention are unsupported by proper evidence, and are in error. As noted above, the Office fails to provide the relevance of Quane to the claims of the presently claimed invention. In turn, as noted above, Quane refers to **in vitro contracture testing** of biopsied skeletal muscle **after** a deleterious clinical event, not genetic testing before exposure to anesthetic drugs. In the Office Action of January 13, 2010 the Office fails to indicate where this teaching is to be found in Quane.

As well, in constructing its hybrid artisan of ordinary skill *i.e.* an anesthesiologist combined with a molecular biologist, the Office makes multiple errors. First, in the Office Action of January 13, 2010 the Office fails to cite statute or case law supporting the Office's speculative creation of an anesthesiologist/molecular biologist ordinary

artisan. Nor has the Office indicated where such artisans of ordinary skill, let alone extraordinary skill, are to be found in the Office's combination of references. Second, the Office fails to consider the claims of the present invention from the perspective of either an anesthesiologist, or a molecular biologist, or the Office's imagined anesthesiologist/molecular biologist at the time the invention was made. Different aspects of the rejection float from one artisan to another. This is improper. The rejection must identify who the artisan is and their requisite skill level. The necessity for this is demonstrated by the fact that the rejection uses inconsistent perspectives at each different turn.

Applicant submits that the Office's failure to identify an artisan of ordinary skill of relevance to the claims of the presently claimed invention is explained by the wide separation between anesthesiology and genome based medicine. Applicant submits herewith Appendix A - "Perioperative Genomics: Anesthesiology Goes Molecular", GenomeLife Magazine, issue 3, November, 2003, page 7. (available at www.genome.duke.edu) (hereinafter "GenomeLife"). GenomeLife notes:

> "According to Schwinn and a growing contingent of forward-thinking anesthesiologists, the tools of "perioperative genomics" may soon be a standard part of the operating-room arsenal used to ensure patient safety. The idea is simple: since millions of common variants (polymorphisms) in our DNA have been catalogued, it should now be possible to examine specific DNA changes in order to predict negative surgical outcomes such as intraoperative bleeding. While the concept may be intriguing, **it is still in its infancy**. A Google search of "perioperative genomics" yields less than two dozen hits (most of those are links to Schwinn and Duke); even a query of the PubMed database generates a mere smattering of scientific references. In part, this is due to the novelty of this approach, but its failure to make much of a splash thus far also reflects **a long-standing separation of the practice of anesthesiology from clinical genetics and genome-based medicine.** Schwinn believes that this divide arose from how traditional anesthesiology is done "in the trenches" as compared to genetics." (GenomeLife, page 7, col. 1.) (Emphasis added.)

And:

> "Looking ahead, Schwinn marvels at the untapped potential of perioperative genomics if it is done right. "If we are both careful and visionary, these types of studies can help us predict perioperative outcomes based on preoperative genomic information. **They could truly revolutionize clinical research**."" (GenomeLife, page 7, col. 2.) (Emphsis added.)

Thus, even well after the filing date of the presently claimed invention, the field was "still in its infancy", and **not**, as the Office argues, in the possession of the Office's artisan of ordinary skill. Similar to Office's impermissible combination of references made in hindsight, Applicant submits that the Office has engaged in making an impermissible combination of ordinary artisans in hindsight.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Response to Office Action Dated June 18, 2007 Applicant submitted the Declaration of Dr. Kirk Hogan. In his Declaration Dr. Hogan (Declaration of Kirk Hogan M.D. Under 37 C.F.R. 1.132, pages 2-3.) explains that prior to the perioperative genomic profile kits of the presently claimed invention, **anesthesiologists of ordinary skill** were **not** aware of, and did **not** use, kits for genomic analysis of single or multiple polymorphisms, genes or diseases. Dr. Hogan explains that:

> "5. For many decades before the perioperative genomic profile kits of the present patent application, anesthesiologists were highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations. Nevertheless, anesthesiologists did not arrive at the kits of the presently claimed invention."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "6. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of single polymorphisms, single genes or single diseases."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "7. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of single polymorphisms, single genes or single diseases.

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "8. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "9. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "11. While the anesthesiologist of ordinary skill has for many decades recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery, anesthesiologists of ordinary skill could not have combined the claimed elements because they lacked the

> requisite appreciation of the technical knowledge to arrive at the perioperative genomic profile kits of the presently claimed invention as a solution to the problems addressed by the presently claimed invention."

In the Office Action of January 13, 2010 the Office does not contest or even address these facts let alone provide contrary evidence.

Applicant notes that expert testimony must be considered, and the testimony that is not simply an expression of an ultimate legal conclusion **is** evidence that cannot be summarily dismissed. Applicant submits that the proper standard is one of ordinary skill in the art, not one of exceptional skill *i.e.*, a researcher or an author of an academic manuscript. Second, elsewhere in the Office Action of January 13, 2010 the Office clearly establishes an anesthesiologist as an artisan of ordinary skill for the purposes of performing an obviousness analysis. (See Office Action of January 13, 2010, pages 9-10.) It is **improper to switch the identity** of the skilled artisan to support an argument when convenient (*i.e.*, when but for the switch, the argument would fail). **This is a fundamental error in the rejection.**

Even if a molecular biologist could be considered an artisan of ordinary skill, and Applicant submits that one could not, the Office provides no evidence that such a molecular biologist would have been motivated to make the Office's combination and thereby arrive at the claims of the present invention. For example, the Office has made no showing that a molecular biologist of ordinary skill would have been motivated to combine component parts configured to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β. Indeed, this is contrary to the art and the evidence in the record. Molecular biologists of ordinary skill did not and would not assemble the clinically relevant claimed markers.

To the contrary, Applicant submits that Dr. Hogan's Declaration provides clear-cut, expert, and uncontested **evidence** that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations "**for many decades**", and that despite this motivation artisans of ordinary skill of any background failed to achieve the presently

claimed invention at the time the invention was made. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Response to Office Action of June 18, 2007 Applicant submitted the Declaration of Dr. Douglas Baird Coursin. In his Declaration, Dr. Coursin explains that there was no suggestion or teaching in the prior art for periperative genomic profiles. Dr. Coursin further explains the **long felt and unmet need** for this solution to the problem of inborn predispositions to complications during anesthesia and surgery, and the unexpected success of the technology. Dr. Coursin is one of the leading anesthesiologists in the country, and has been for many years. Dr. Coursin explains that skilled artisans, such as anesthesiologists, have as a primary mission to solve the problem solved by the present invention. Yet even with this long-felt need and years of searching by innumerable practitioners, no one solved this long-felt need using the approach of the present invention. In the Office Action of January 13, 2010 the Office does not contest or even address these facts.

In a situation like the present one, there may be no better evidence of non-obviousness than the **failure of an entire field** to solve their primary problem, even with a wealth of information and technology known in the literature. As Dr. Coursin notes:

> "However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made." (Declaration of Douglas Baird Coursin, M.D. Under 37 C.F.R. 1.132, page 3.)

In the Office Action of January 13, 2010 the Office does not contest or even address these facts. Applicant notes that the field failed to realize the solution because

the solution was not obvious to these skilled artisans. These skilled artisans would not, and did not, see the combination the Office proposes that they should have and would have seen.

Applicant submits that Dr. Coursin's Declaration provides **clear-cut, expert, and uncontested evidence** that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations for 26 years "and well before". Dr. Coursin's Declaration provides evidence that the need was persistent and recognized by those of ordinary skill in the art.

Applicant submits that the Office's rejection is based on hindsight knowledge of the invention wherein the Office has assumed what skilled artisans *should have* thought of the invention in view of numerous disparate pieces of prior art. In making the rejection, the Office (*i.e.*, not one of skill in the art, and who is in possession of hindsight knowledge of the invention), has *seen* an invention that the entire world of skilled artisans, focused for many years on the exact problem solved by the invention, had failed to see. Artisans, of ordinary and extraordinary skill in the field, who have devoted their careers to solving this problem, failed to put together the Office's combination of references, and failed to solve the problem. The only logical explanation is that the invention is non-obvious. In the Office Action of January 13, 2010 the Office does not contest or even address these facts.

Notably missing from the Office's rejection is placement in the hands and minds of the appropriate skilled artisans of: 1) the prior art of record (is this the type of work one skilled in the art would have reviewed in assessing the problem?); and 2) the mental and experimental process for modifying the art to arrive at the invention (even if they would have reviewed the cited art, would they have put the pieces together and modified the pieces appropriately?). At no point in the Office Action of January 13, 2010 does the Office provide **evidence** of the handling of the references in the hands and minds of the **appropriate skilled artisan**. Regardless, even if the Office had done this, the evidence of long-felt but unresolved need demonstrates that skilled artisan did not, and would not, arrive at the invention. If it were obvious, they would have done it years before the filing

of the present application. In the Office Action of January 13, 2010 the Office does not contest or even address these facts.

The Supreme Court specifically states:

> "Often it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; **and the background knowledge possessed by a person having ordinary skill in the art**, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." (*KSR Int'l Co. v. Teleflex, In.,* 550 U.S., 127 S. Ct. 1727 (2007).) (Emphasis added.)

Applicant asserts that in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of 8 prior art elements (*vs.* 2 prior art references in *KSR v. Teleflex*), the Office has clearly failed to identify the reason why a person of ordinary skill in the art would have made the combination in the manner claimed. In making such a reconstruction, the Office may only take into account the common knowledge which was within the level of ordinary skill at the time the claimed invention was made, and may not include, as here, knowledge gleaned only from the Applicant's disclosure or unsupported assumptions about the mindset of the skilled artisan. (See *In re McLaughlin*, 443 F/2d 1392, 170 USPQ 209 CCPA, 1971.) The determination of whether a combination is a predictable variation of the prior art must be evaluated from the perspective of the person of ordinary skill in the art at the time claimed invention was made. Dr. Hogan's and Dr. Coursin's Declarations provide material evidence that Office's speculations regarding the level of ordinary skill are in clear error. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

In the Office Action of January 13, 2010 the Office notes:

> "With respect to kits, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come prepared." (Office Action of January 13, 2010, page 31.)

In relying upon these arguments to support a prima facie case of obviousness, the Office has made a number of errors. First, The Office's acknowledgment of the benefits of the claimed invention made after the Office was in possession of the specification and claims does not, and cannot, substitute for substantial **evidence** of what an artisan of ordinary skill would or would not have been motivated to do at the time the invention was made. To the contrary, the in the Office Action of January 13, 2010 the Office improperly persists in asserting new standards of the ordinary artisan's motivation to combine references *i.e.*, to "save time and money", and "to avoid any fatal reaction." In *In re Sang Su Lee* the Court of Appeals for the Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Office.[28] On multiple occasions in the prosecution of the present application the Examiner has had the opportunity to address this holding, and has never done so. These facts were pointed out to the Office in the Appellant's Brief of September 24, 2009. The Office Action of January 13, 2010 is unresponsive to these facts. Applicant submits that the Office's improper combination of references, and failure to respond to numerous facts in the Appellant's Brief filed in response to the Final Office Action of March 24, 2008 preclude a finding of prima facie obviousness of the claims.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

2. The cited references do not teach all elements of the presently claimed invention

Applicant submits that the Office's combination of references fails to teach all elements of the claims. The Office has never indicated where in the Office's references, either alone or in combination, such kits (*e.g.*, kits with component parts configured such

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[28] *In Re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002).

that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ* so as to generate a genomic profile for use in selecting a perioperative course of action for said subject) are to be found.

Applicant notes that whether or not the **kits of the presently claimed invention** are to be found in the Office's combination of references is at issue, not the presence or absence of **kits as a generic concept** in the art. Applicant submits that kits of the presently claimed invention are clearly not to be found in the Office's combination of references. Ahern teaches kits for, for example: expression of proteins from cloned genes; for labeling DNA or RNA probes with radioisotopes or fluorescent tags; for labeling oligonucleotides by conjugation with alkaline phosphatase; for small-scale purifications; for isolating cells from whole blood for cytotoxicity assays; for painting chromosomes with fluorescent dyes; for cryopreserving mouse embryos; and for signal transduction research.

Ahern does **not** teach or suggest kits sufficient to detect variation in one gene. Ahern does **not** teach or suggest kits sufficient to detect variation in two genes. Ahern does **not** teach or suggest kits sufficient to detect variation in two or more genes selected from a group of genes, or in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNA1S, MTHFR, MTR, MTRR, CB, TNFα and TNFβ.* These missing elements were pointed out to the Office in the Appellant's Brief filed September 24, 2009, page 22. In the Office Action of January 13, 2010 the Office is unresponsive to these facts. Indeed, to the extent that Ahern contemplates characterization of DNA, **Ahern discourages use of such kits:**

> "Some tasks … such as constructing genomic libraries, designing primer sets for sequencing, or synthesizing nucleic acids or peptides … are so daunting that for many scientists it makes more sense to hire out." (Ahern, page 5).

Clearly Ahern clearly directs scientists away from kits for the specific purpose of the claims *i.e.,* Ahern directs scientists to hire others for DNA characterization rather than to use kits. Accordingly, the Office's reference teaches directly away from both the Office's combination of references, and from the presently claimed invention.

In view of the above, the Applicant respectfully requests that this rejection be withdrawn.

Morever, none of the Office's references, alone or in combination, teach or suggest the element of reagents that are sufficient to detect the presence or absence of variant alleles **in each of** *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β (*i.e.*, none provide the claimed **combination**). Applicant submits that the Office Action of January 13, 2010 fails to examine, or even recognize, this element of claims 106-107, or to explain why the claimed combination itself is obvious compared, for example, to other combinations.

In view of the above, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 662-1277.

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/David A. Casimir/

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